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09/458,014	12/10/1999	JACQUES DUMAS	BAYER11-C1	8328

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/458,014	DUMAS ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,28,30,38,44,45,50,51,53,55 and 58* is/are pending in the application.

4a) Of the above claim(s) *53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 2/2/09. Claim(s) 5-7, 9-27, 29, 31-37, 39-43, 46-49, 52, 54, 56-57 have been cancelled. Claim(s) 1-4, 8, 28, 30, 38, 44-45, 50-51, 53, 55, 58 are pending. Claim(s) 1, 8, 38, 44-45, 53 been amended. Claim(s) 53 has been withdrawn. Claim(s) 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 are examined herein.

Applicant's arguments with respect to the obviousness double patenting rejection over US Patent 6,344,476 B1 of the last Office Action have been fully considered are persuasive, therefore the rejection is hereby withdrawn. The obviousness double patenting rejection over Application No. 09/776,935 of the last Office Action is withdrawn because the referenced case has been abandoned. The remaining obviousness double patenting rejections are maintained for reasons of record and repeated below for Applicant's convenience.

Applicant's arguments with respect to the 112 rejection of the last Office Action have been fully considered but found not persuasive. The rejection of the last Office Action is maintained for reasons of record and modified below as a result of the new claim amendments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8, 28, 30, 44-45, 50-51, 55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 50-74 of copending Application No. 09/838,286; claims 1-16 of copending Application No. 09/947,761; claims 34-36, 39-42, 44 of copending Application No. 10/361,858; claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426; claims 1-69 of copending Application No. 10/848,567; claims 1-34, 37-41 of copending Application No. 11/932,548; claims 1-16 of copending Application No. 12/181,032. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claimed and referenced claims are an obvious variation of a method of treating rheumatoid arthritis by administering a compound of formula I, where the there is substantial overlap between both formulas.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant argues that the rejections over obviousness double patenting are premature since allowable subject matter has not been identified in this application.

Examiner reminds Applicant that no matter whether the instant claims are allowable or not, the instant claims must be examined for any possible obviousness double patenting rejections and accordingly must be applied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method for the treatment of a disease mediated by p38 other than cancer, for example rheumatoid arthritis, comprising administering a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the breadth of the claims; (4) the amount of direction or guidance presented; (5) the predictability or unpredictability of the art; (6) the relative skill of those in the art; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims are drawn to an invention which pertains to a method for the treatment of a disease mediated by p38 other than cancer, such as rheumatoid arthritis, comprising administering a compound of formula I.

(2) State of the Prior Art: The state of the art regarding p38 inhibition has shown to inhibit both cytokine production (TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). Clinical studies have linked TNFα production to a number of inflammatory and/or immunomodulatory diseases. There is no indication that such a link actually translates to treatment of the disease. Therefore, the same argument can be applied to p38 inhibition. Accordingly, the same argument is applied to rheumatoid arthritis. Even if we were to assume that an inhibition of p38 would lead to the desired inhibition of TNFα, a link between TNFα production and rheumatoid arthritis doesn't mean that any inhibition of TNFα would treat rheumatoid arthritis. It is further noted that the specification likewise indicates that TNFα production is linked to numerous other diseases.

(3) Breadth of Claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass virtually every disease or disorder that is mediated by p38 kinase. Furthermore, p38 kinase is disclosed to inhibit both cytokine production (TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). Therefore, the invention is complex because it involves any disease or disorder related to these cytokines or enzymes as being within the scope of this invention. Furthermore, the claims encompass any urea illustrated by the broad generic structure of formula I. The nature of the invention is complex in that it potentially encompasses a vast number of compounds in excess of 100 million compounds.

(4) Guidance of the Specification: The guidance of the specification discloses a pathway between inhibition of p38 and various inflammatory and/or immunomodulatory diseases through cytokine production (TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). The specification does not disclose how to determine whether a disease or disorder can be treated by p38 inhibition, it only discloses that the two are linked together. As a result, one of ordinary skill in the art would be forced to perform an exhaustive search for the embodiments of any drug having the function recited in the instant claims suitable to practice the invention. Furthermore, one of ordinary skill in the art would have to determine not only which compounds inhibit p38, but which compounds are therapeutically effective on a p38 mediated disease. The specification shows examples of *in vitro* p38 inhibition but does not provide any raw

data or what specific compounds were tested. The *in vivo* study was not performed on subjects with any diseases or disorders.

(5) The Predictability or Unpredictability of the Art: The invention is directed to a method for the treatment of a disease mediated by p38 other than cancer comprising administering a compound of formula I. Treatment of a disease involves many biochemical pathways mediated by many different proteins. It is not possible to predict the efficacy in the treatment of a disease simply by inhibition of p38.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring

with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(6) The Relative Skill of those in the Art: One of ordinary skill in the art knows how to inhibit p38 and how to effectively treat various inflammatory and/or immunomodulatory diseases, but does not know how to treat diseases that are not inflammatory or immunomodulatory by nature by inhibiting p38.

(7) Working Examples: The specification lacks any working examples of treating a p38 mediated disease, let alone rheumatoid arthritis, comprising administering a compound of formula I. The only examples are drawn to an *in vitro* p38 kinase inhibition assay and *in vivo* inhibition of TNFα in mice. Examiner notes that there is no raw data for any of the disclosed compounds for either of these examples. Moreover, the mice are not disclosed to have a p38 mediated disease or disorder, therefore no disease is being treated in the examples.

(8) The Quantity of Experimentation Necessary: The specification fails to provide sufficient support for the broad use of any compound represented by formula I in a method for the treatment of a disease mediated by p38 other than cancer, such as rheumatoid arthritis. A large quantity of experimentation would be needed in order to discover what diseases or disorders can be treated by inhibition of p38 and to what extent. Nor does it provide information to practice the claimed invention, absent undue experimentation. As a result, one of ordinary skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in

the instant claims suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit p38, but which compounds actually have efficacy in treating rheumatoid arthritis.

Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Response to Arguments

Applicant argues that the specification provides more than it needs to satisfy the requirement of 112, first paragraph. For example, general and specific methods of preparing the compounds are given on pg. 21-23, 27-71, and in the examples. Dosage forms, ranges, and methods of administration are given on pg. 23-26. Methods for assessing the activity of the compounds via in vitro raf Kinase assays and in vivo assays are provided on pg. 103-104. The specification also discloses that inhibitors of p38 are active in animal models of TNFα production, including a murine lipopolysaccharide (LPS) model of TNFα production.

This is not persuasive because the specification does not provide any experimentation of any compounds in an accepted specific rheumatoid arthritis assay. Additionally, the specification does not provide an assertion that any of the referenced articles specifically describe the inhibition of TNFα, via inhibition of p38 kinase, leads to the treatment of rheumatoid arthritis. The specification merely states that a link exists

between TNFα production and/or signaling to a number of diseases including rheumatoid arthritis. What is missing from the specification is sufficient direction and guidance for determining which compounds of formula I that are found to inhibit p38 kinase activity do so in a manner sufficient to inhibit TNFα to a degree that causes a therapeutic effect in rheumatoid arthritis as claimed. Without this guidance, undue experimentation of a skilled artisan would be required to make and use the claimed invention.

Applicants argue against the enablement rejection by claiming that a link exists between TNFα and rheumatoid arthritis, highlighted by the Badger reference. Applicants also corroborate their argument by referring to the in vitro raf kinase assays and in vivo assays in the specification, which is allegedly routine in the field to correlate inhibition of p38 to therapeutic treatment of various diseases. Examiner was reminded that no objective evidence has been presented and also that an example is not required for compliance with an enablement requirement.

This is not persuasive because although there may be link between TNFα or p38 and various diseases this does not correlate to actually treating a disease in any therapeutic sense. In fact, inhibition of p38 is not well known in the field to be correlated to any particular disease. The Badger reference is an isolated reference that cannot be taken as the standard for the state of art concerning inhibition of p38 and the treatment of various diseases. The reference does not provide any evidence describing the activity of a pyridinyl imidazole p38 kinase inhibitor are applicable to the aryl ureas of the claimed formula I. Further, the abstract does not provide the missing guidance

regarding how to determine which compounds of formula I that are found to inhibit p38 kinase activity do so in a manner sufficient to inhibit TNFα to a degree that results in the treatment of rheumatoid arthritis.

The specification does not disclose how one of ordinary skill in the art would determine every known disease associated with p38, let alone effectively to treat that disease with a p38 inhibitor considering various factors such as side effects, toxicity, and dosing. There is no indication that such a link actually translates to the treatment of the disease. There is no mention of activity data for any of the disclosed compounds. Further, in vitro raf kinase assays and in vivo assays are not specific to rheumatoid arthritis. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass virtually every disease or disorder that is mediated by p38 kinase.

It is noted that the specification also lacks any factual evidence of actual therapeutic treatment of a disease associated with p38. It is not well established in the field to correlate inhibition of p38 to actual treatment of a disease. Moreover, there is no raw data for any of the disclosed compounds in the examples of the specification. The mice are not disclosed to have a p38 mediated disease or disorder, therefore no disease is being treated in the examples.

Applicant also provides additional references (Exhibits B and C) to support the link between p38 inhibition and the treatment of disease as recognized by others.

This is not persuasive because these references were published after the application filing date. These later-published articles do not establish that the Examiner erred in determining the state of the art at the time of invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/YONG S. CHONG/
Primary Examiner, Art Unit 1617

YSC